PATENT COOPERATION TREATY



# PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference<br>38430 | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No.<br>PCT/BR 03/00120 | International filing date *(day/month/year)*<br>22.08.2003 | Priority date *(day/month/year)*<br>30.08.2002 |
| International Patent Classification (IPC) or both national classification and IPC<br>A61K31/137 | | |
| Applicant<br>FUNDAÇAO DE AMPARO A PESQUISA DO ESTADO DE SAO P.. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 17 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 12.03.2004 | 03.12.2004 |
| Name and mailing address of the international preliminary examining authority:<br>European Patent Office<br>D-80298 Munich<br>Tel. +49 89 2399 - 0 Tx: 523656 epmu d<br>Fax: +49 89 2399 - 4465 | Authorized Officer<br>Elliott, A<br>Telephone No. +49 89 2399-8218 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/BR 03/00120

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

| | |
|---|---|
| 3-38 | as originally filed |
| 1, 2, 2a, 2b, 2c, 2d | filed with telefax on 05.08.2004 |

**Claims, Numbers**

| | |
|---|---|
| 1-92 | filed with telefax on 05.08.2004 |

**Drawings, Sheets**

| | |
|---|---|
| 1/11-11/11 | as originally filed |

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 59-79

   because:

   ☒ the said international application, or the said claims Nos. 59-79 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 1-92 |
| | No: | Claims | - |
| Inventive step (IS) | Yes: | Claims | 1-92 |
| | No: | Claims | - |
| Industrial applicability (IA) | Yes: | Claims | 1-58, 80-92 claims 59-79 : no opinion - methods of treatment |
| | No: | Claims | - |

2. Citations and explanations

**see separate sheet**

The application relates to cyclic palladium compounds where the palladium has coordinated to it one or both of the phosphine groups attached to both cyclopentadiene rings of ferrocene. Also attached to the palladium atom is a carbon atom which is part of a carbon-carbon double bond and a group 15 or 16 atom attached via a dative bond, the carbon atom and datively bound atoms forming a ring together with the palladium. If only one phosphine ligand is attached to the palladium, then a further group is attached to the palladium. Also encompassed are compounds where each phosphine ligand is bonded to a separate palladium atom. The compounds are preferably N,N-dimethyl-1-phenylethylamine (dmpa), N,N-dimethylbenzylamine, alkyl pyridinyl-phenyl-ethene and 1-phenyl-3-N,N-dimethylamine propene derivatives. The compounds find use in the inhibition of the activity of proteins or enzymes and are useful in the treatment of diseases or disorders associated with these enzymes or proteins, especially cancer.

The following documents will be referred to in this report:

D1: Journal Of Organometallic Chemistry (3-1-2003), 665(1-2), 76-86
D2: Polyhedron (1-10-2002), 21(22), 2309-2315
D3: European Journal Of Inorganic Chemistry (9-2002), (9), 2389-2401
D4: New Journal Of Chemistry (25-1-2002), 26(1), 105-112
D5: Journal Of Organometallic Chemistry (3-12-2001), 637-639, 577-585
D6: Polyhedron (15-11-2001), 20(24-25), 2925-2933
D7: Transition Metal Chemistry (2001), 26(4-5), 570-573
D8: European Journal Of Inorganic Chemistry (9-2000), (9), 2055-2062
D9: Inorganica Chimica Acta (15-3-2000), 299(2), 164-171
D10: Zeitschrift Fuer Naturforschung, B: Chemical Sciences (1998), 53(4), 448-458
D11: Journal Of The Chemical Society, Dalton Transactions (1998), (7), 1241-1247
D12: Organometallics (2-7-1997), 16(18), 4023-4026
D13: US-A-5880149
D14: Journal Of Medicinal Chemistry (23-4-1998), 41(9), 1399-1408
D15: Inorganic Chemistry (28-8-1996), 35(18), 5181-7
D16: Journal Of Medicinal Chemistry (26-11-1993), 36(24), 3795-3801

## III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

No unified criteria exist under the PCT for assessing the industrial applicability of the subject-matter of claim **59-79** directed to methods of medical treatment. Hence it is not possible at this stage of the proceedings to give an opinion as to the industrial applicability of these claims.

**V Reasoned statement under Art 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement**

i. ***Novelty (Article 33(2) PCT)***

The subject-matter of claims 1-92 is to be regarded as novel on the following grounds:

Originally claims 2-4 as originally filed were objectionable to on the grounds of documents D4-D12 disclosing compounds falling under the scope of the claims (cf. relevant passages indicated in the International Search Report - for a more detailed analysis of these documents please see the written opinion issued during the international proceedings).

Claims 2 and 3 have been amended to incorporate subject-matter from original claims 4 and 5 to overcome these novelty objections. The compounds now on file are novel over the prior art. The subject-matter of claims 5-92 directed to the uses of the compounds and medical treatment involving their use are mutis mutandis also to be regarded as novel.

ii. ***Inventive Step (Article 33(3) PCT)***

As closest prior art are to be regarded the disclosures of documents D13-D16 as these address the uses of the present application with structurally similar palladium compounds.

The object of the present application can be seen as the provision of further compounds for use in treating cancer or in inhibiting certain proteins or enzymes involved in the metastasis or development of cancer.

The subject-matter of the claims in their amended format is to be regarded as the result of an inventive step on the following grounds:

although documents D6-D8 all mention in their introductory portion that it is already known that cyclometallated palladium(II) complexes are useful as antitumour drugs, the compounds now being claimed are new cyclometallated palladium complexes unknown at the date of filing - these compounds are structurally far enough removed from the cyclometallated palladium compounds known at the date of filing and cannot

be seen as having been suggested as possible candidates to solve the problem posed by the present application.

## VI Certain documents cited

Documents D1-D3 were published in the priority interval of the present application and, as such, are not to be considered as prior art according to Rule 64.3 PCT.

The disclosures of these documents could, however, become prior art should the priority claimed for the present application not turn out to have been validly claimed.

## VIII Certain observations on the international application

Concerning the amendments made during the international proceedings, it would have been simpler and much clearer if the applicant had merely drawn the 3 possible structures which the combination of C and Y can represent (with regard to structures 4A and 4B, it is clear that the Cl atoms should be H atoms).

# CYCLIC PALLADIUM COMPOUNDS HAVING COORDINATED THERETO BIS(DIPHENYLPHOSPHINE) FERROCENE LIGANDS WHICH INHIBIT THE ACTIVITY OF PROTEINS AND ENZYMES AND TREATMENT OF DISEASES AND DISORDERS ASSOCIATED THEREWITH

## FIELD OF THE INVENTION

The invention refers to cyclopalladated compounds containing bis-diphenylphosphine-ferrocene coordinated ligands and their analogues as active inhibitors for peptides and enzymes comprising serine peptidase, cysteine-protease, metallo-protease and endopeptidase families, many of which are essential for the route of growth and metastasis of malignant tumors. Acting over these enzymes and taking part of insertions with DNA molecules, these compounds modulate the immunological system.

## BASICS OF THE INVENTION

The study of inorganic chemistry in the pharmaceutical field has been receiving special attention from researchers due to the clear advantages of its use over traditional medicines for the treatment of a series of pathologies.

The best-studied inorganic pharmaceutical is cisplatin, a drug which has been clinically used for the treatment of a wide range of tumors. It is believed that its action occurs by means of interaction with DNA, thus inhibiting the proliferation of tumor cells (Lippard, *Science* 218: 1075-1082 (1982); Rosenberg, *Nature* 222: 385 (1969); Cleare el al, *Bioinorg. Chem.* 2: 187 (1973)). This compound is efficient for the combat against various kinds of tumors and is highly cytotoxic, being also extensive to normal cells (Ebert, U., Loffler, H., Kirch, W., *Pharmacology & Therapeutics*, 74: (2) 207-220 1997; Spencer C. M., Goa K. L., *Drugs*, 50: (6) 1001-1031 DEC 1995).

Gold-based complexes have been used for the treatment of arthritis and its route of action involves the linkage to a thiol group of proteins, thus inhibiting the appearance of disulphite bridges, which may cause their denaturation.

Metal complexes of cobalt have also been already pointed out as presenting antiviral, antitumor and antimicrobial activity, besides anti-inflammatory properties.

Metal compounds which can change or link to functional sites of proteins resulting in the inactivation of its biological activities are described by the U. S. Patent 5,880,149. The document discloses some palladium complexes (pertaining to the class of coordination compounds), as irreversible inhibitors of cysteine-proteases, as powerful antitumor drugs and as very efficient drugs in numerous infectious processes, in which the route of action of cysteine-proteases is involved. As an example, we mention the enzymatic inhibition caused by palladium complexes over Cathepsins B, H, J, L, N, S, T and C and over the Interleukine Converter Enzyme (ICE), constituting active drugs against Amebiasiss, Trypanosomiasis and Leishmaniosis. The U. S. patent is the latest work

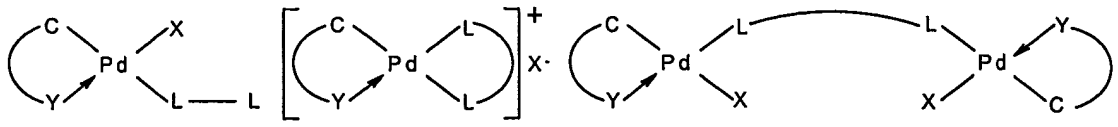
published on the development and routes of action of antitumor drugs, involving compounds of the chemical element palladium.

## DISCLOSURE OF THE INVENTION

The invention deals with innovative palladium complexes (pertaining to the family of organometallic compounds), containing a Sigma C - PD bond and a coordination linkage Y → Pd, giving origin to an organic cycle, for which reason these compounds are designated as cyclopalladated, also known as palladacycles.

The compounds covered by the invention can be defined by the generic structures A, B or C of the Scheme 1 below:

## SCHEME 1



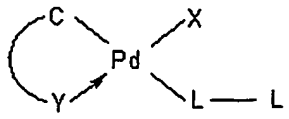

A B C

in which:

- **X** represents an element chosen from the following groups:
  halogen (Cl, F, Br, I);
  pseudo-halogen ($N_3$, NCO, NCS, SCN); or
  acetate ($H_3C$-$COO^-$); and
- **Y** represents an element from the group V or VI of the Periodic Table, e. g. N, P, As, Sb, Bi, O, S, Se, Te;
- **C** represents an atom of carbon with $sp^2$ or $sp^3$ hybridization, covalently linked to the atom of palladium. The ring containing C, Y and D can be constituted of three to eight atoms.
- Between C and Y, represented by a curved line, there is a succession of atoms designated as cyclopalladated ring, constituted of three to eight atoms, including the atom of palladium. Typically, not excluding any other way, said atoms are chosen from carbon, nitrogen, oxygen or sulphur. Each one of these atoms constituting the ring can, on the other hand, be linked to other atoms or groupings, forming variable structures external to the ring, linear or cyclic, for which no specific limitations are known by the Applicant.
- L represents a coordinated ligand which is a donating atom from the group V of the Periodic Table (N, P, As, Sb, Bi) within a bis-diphenylphosphine-ferrocene compound as detailed by Scheme 2 below, with the schematic representation L-L indicating the presence of two linkers L within the structure of said bis-diphenylphosphine-ferrocene compound, while R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 represent individually the following radicals, which can be present in any order: hydrogen (H), alkyl, aryl, dienyl, alkoxy, siloxy, hydroxy (OH), amino ($-NH_2$), imide, halogen (F, Cl, Br, I), imino, nitro ($-NO_2$).

## CLAIMS

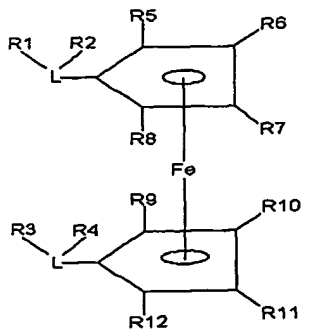
1. CYCLOPALLADATED COMPOUND, which is an organometal compound comprising palladium, a Sigma C - Pd bond and a coordination bond Y → Pd, originating an organic cycle with formula corresponding to the structures below:




in which:

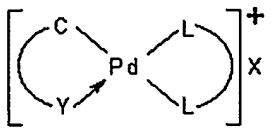
- X represents an element chosen from the following groups: halogen (Cl, F, Br, I); pseudo-halogen ($N_3$, NCO, NCS, SCN); or acetate ($H_3C$-$COO^-$); and
- Y represents an element from the group V or VI of the Periodic Table, e. g. N, P, As, Sb, Bi, O, S, Se, Te;
- C represents an atom of carbon with $sp^2$ or $sp^3$ hybridization, covalently bonded to the atom of palladium; the ring containing C, Y and D can be constituted of three to eight atoms;
- between C and Y, represented by a curved line, there is a succession of atoms designated as cyclopalladated ring, constituted of three to eight atoms, including the atom of palladium; typically, not excluding any other way, said atoms are chosen from carbon, nitrogen, oxygen or sulphur; each one of these atoms constituting the ring can, on the other hand, be linked to other atoms or groupings, forming variable structures external to the ring, linear or cyclic, for which no specific limitations are known by the Applicant;
- L represents a coordinated ligand which is a donating atom from group V of the Periodic Table (N, P, As, Sb, Bi) within a bis-diphenylphosphine-ferrocene compound as detailed by Scheme 2 below, with the schematic representation L-L indicating the presence of two linkers L within the structure of said bis-diphenylphosphine-ferrocene compound, while R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 represent individually the following radicals, which can be present in any order: hydrogen (H), alkyl, aryl, dienyl, alkoxy, siloxy, hydroxy (OH), amine (-NH2), imide, halogen (F, Cl, Br, I), imine, nitro (-NO2);

**SCHEME 2**



or one of its pharmaceutically acceptable salts or adducts.

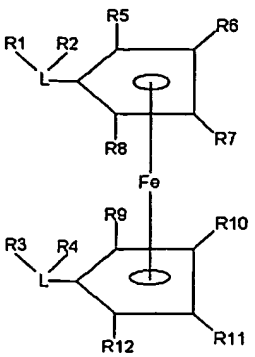
2. CYCLOPALLADATED COMPOUND, which is an organometal compound comprising palladium, a Sigma C - Pd bond and a coordination bond Y → Pd, originating an organic cycle with formula corresponding to the structure below:




in which:

- X represents an element chosen from the following groups: halogen (Cl, F, Br, I);pseudo-halogen ($N_3$, NCO, NCS, SCN); or acetate ($H_3C$-$COO^-$); and
- Y represents an element from the group V or VI of the Periodic Table, e. g. N, P, As, Sb, Bi, O, S, Se, Te;
- C represents an atom of carbon with $sp^2$ or $sp^3$ hybridization, covalently bonded to the atom of palladium; the ring containing C, Y and D can be constituted of three to eight atoms;
- between C and Y, represented by a curved line, there is a succession of atoms designated as cyclopalladated ring, constituted of three to eight atoms, including the atom of palladium; typically, not excluding any other way, said atoms are chosen from carbon, nitrogen, oxygen or sulphur; each one of these atoms constituting the ring can, on the other hand, be linked to other atoms or groupings, forming variable structures external to the ring, linear or cyclic, for which no specific limitations are known by the Applicant;
- L represents a coordinated ligand which is a donating atom from group V of the Periodic Table (N, P, As, Sb, Bi) within a bis-diphenylphosphine-ferrocene compound as detailed by Scheme 2 below, with the schematic representation L-L indicating the presence of two linkers L within the structure of said bis-diphenylphosphine-ferrocene compound, while R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 represent individually the following radicals, which can be present in any order: hydrogen (H), alkyl, aryl, dienyl, alkoxy, siloxy, hydroxy (OH), amine (-NH2), imide, halogen (F, Cl, Br, I), imine, nitro (-NO2);

**SCHEME 2**



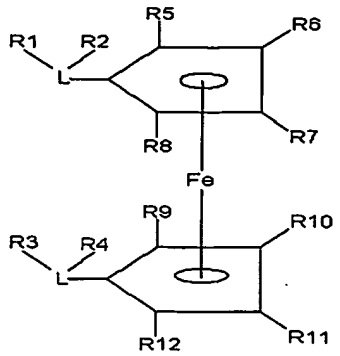

or one of its pharmaceutically acceptable salts or adducts.

3. CYCLOPALLADATED COMPOUND, which is an organometal compound comprising palladium, a Sigma C - Pd bond and a coordination bond Y → Pd, originating an organic cycle with formula corresponding to the structures below:


in which:

- X represents an element chosen from the following groups: halogen (Cl, F, Br, I);pseudo-halogen ($N_3$, NCO, NCS, SCN); or acetate ($H_3C$-$COO^-$); and
- Y represents an element from the group V or VI of the Periodic Table, e. g. N, P, As, Sb, Bi, O, S, Se, Te;
- C represents an atom of carbon with $sp^2$ or $sp^3$ hybridization, covalently bonded to the atom of palladium; the ring containing C, Y and D can be constituted of three to eight atoms;
- between C and Y, represented by a curved line, there is a succession of atoms designated as cyclopalladated ring, constituted of three to eight atoms, including the atom of palladium; typically, not excluding any other way, said atoms are chosen from carbon, nitrogen, oxygen or sulphur; each one of these atoms constituting the ring can, on the other hand, be bonded to other atoms or groupings, forming variable structures external to the ring, linear or cyclic, for which no specific limitations are known by the Applicant;
- L represents a coordinated ligand which is a donating atom from group V of the Periodic Table (N, P, As, Sb, Bi) within a bis-diphenylphosphine-ferrocene compound as detailed by Scheme 2 below, with the schematic representation L-L indicating the presence of two linkers L within the structure of said bis-diphenylphosphine-ferrocene compound, while R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 represent individually the following radicals, which can be present in any order: hydrogen (H), alkyl, aryl, dienyl, alkoxy, siloxy, hydroxy (OH), amine (-NH2), imide, halogen (F, Cl, Br, I), imine, nitro (-NO2);

SCHEME 2




or one of its pharmaceutically acceptable salts or adducts.

4. CYCLOPALLADATED COMPOUND of any of claims 1 to 3, which is selected from the group comprising N,N-dimethyl-1-phenethylamine (dmpa) and N,N-dimethyl-benzilamine derivatives, alkines pyridinyl-phenyl-ethine or 1-phenyl-3-N,N-dimethylamine-propine or one of its pharmaceutically acceptable salts or adducts.

5. CYCLOPALLADATED COMPOUND of claim 4, which is N,N-dimethyl-1-phenethylamine (dmpa).

6. COMPOUND of any of claims 1 to 5, which inhibits the activity of proteins linked to disorders or diseases.

7. COMPOUND of claim 6, in which the protein is an enzyme.

8. COMPOUND of claim 7, in which the enzyme comprises enzymes from the cysteine-protease, serine peptidase and metallo-protease families.

9. COMPOUND of claim 8, in which the cysteine-proteases comprise Cathepsins B, H, J, L, N, S, T and C (dipeptidyl-peptidase-I), Interleukine Converter Enzyme (ICE), neutral proteases activated by calcium, Calpaine I and II, endopeptidases, viral cysteine-proteases, such as cardiovirus endopeptidase, adenovirus endopeptidase and aphthovirus endopeptidase, and essential proteases for the life cycle of parasites such as proteases from *Plasmodium*, *Entamoebas*, *Onchoceras*, *Leishmanias*, *Haemonchus*, *Dictyostelium*, *Therilerium*, *Schistosoma* and *Tripanosoma* species.

10. COMPOUND of claim 9, in which the enzyme is Cahtepsin B, Cruzaine and Interleukine-1β Converter Enzyme.

11. COMPOUND of claim 8, in which serino-peptidases comprise dipeptidyl-peptidase IV, acylaminacyl-peptidase and oligopeptidase B prolyl-oligopeptidase and Cathepsin D.

12 COMPOUND of claim 11, in which the enzyme is Cathepsin D.

13. COMPOUND of claim 8, in which metallo-proteases comprise angiotensin converting enzyme, collagenases, stromelisines, membrane type metallo-protease and genatinases.

14. COMPOUND of any of claims 1 to 3, which is intended to treat disorders and diseases linked to proteins and enzymes.

15. COMPOUND of claim 14, in which the diseases comprise diseases caused by tissue degradation such as arthritis, muscle distrophy, tumor invasion, glomerulonephrithis, bone infections by parasites, parasitomies, periodontal diseases and tumor metastasis; heart diseases involving the degradation of atrial natriuretic factor; inflammatory diseases, such as e. g. bronchitis, arthritis rheumatoid, osteoporosis, acute pancreatitis and cancer progressions; disorders such as amnesia, control of depression and blood pressure; diabetes, trypanosomiasis, Chagas disease, food disorders, bullimia nervosa and anorexia; alcoholism, diseases related to the production of cytokines and cytokine receptors, such as interleukine-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), interferon-gamma (INFN-gamma), IL-1 antatonist receptor (IL-1 RA), IL-10 and growth stimulation factor for granulocyte-macrophage colonies (GM-CSF), psychological stress, combat against infections caused by HIV virus (AIDS); inflammatory diseases of the Central Nervous System causing mieline degradation, including Multiple Sclerosis and autoimmune Encephalomielitis; cancer tumors, autoimmune diseases, tumors comprising breast, marrow, adenomas, thyroid, melanoma, gastric, bowel, gullet and thyroid tumors and neuroblastomas.

16. COMPOUND of claim 15, in which the diseases are ascitic or solid tumors, particularly breast, marrow, adenomas, thyroid, gastric, bowel, gullet, thyroid tumors and neuroblastomas.

17. COMPOUND of any of claims 1 to 6, which inhibits young bone marrow cells from entering cell division (S stage).

18. COMPOUND of any of claims 1 to 6, which is antiangiogenic.

19. COMPOUND of any of claims 1 to 6, which is antimetastatic.

20. COMPOUND of any of claims 1 to 6, which is useful to complement radio therapy treatments.

21. COMPOUND of claim 1, which interacts with the DNA.

22. COMPOUND of claim 1, which is an immunomodulator.

23. COMPOSITION comprising at least one compound of any of claims 1 to 22 or one of its pharmaceutically acceptable salts or adducts.

24. COMPOSITION of claim 23, which comprises about 0.001 to 99% of the full weight of the composition of the compound or one of its salts or adducts, and at least one pharmaceutically acceptable carrier.

25. COMPOSITION of claim 23, which comprises about 0.01 to 70% of the full weight of the composition of the compound or one of its salts or adducts, and at least one pharmaceutically acceptable carrier.

26. COMPOSITION of claim 23, which comprises about 0.1 to 40% of the full weight of the composition of the compound or one of its salts or adducts, and at least one pharmaceutically acceptable carrier.

27. COMPOSITION of claim 23, which additionally comprises a solvent.

28. COMPOSITION of claim 27, in which the solvent is DMSO.

29. COMPOSITION of claim 23, which is presented in solid dosage forms, such as capsules, tablets or powders, or in liquid dosage forms, such as elixirs, syrups, emulsions, solutions, suspensions, mixtures and infusions.

30. COMPOSITION of claim 29, in which the formulations are scheduled or delayed release.

31. COMPOSITION of claim 29, in which its administration is made by means comprising oral, subcutaneous, intravenous, intranasal, transdermal, intraperitoneal, topic, intramuscular, intralung, vaginal, rectal, intraocular or sublingual means, systems to supply liposomes.

32. COMPOSITION of claim 31, in which its administration is made by injectable means, particularly intraperitoneal.

33. COMPOSITION of claim 32, which comprises particularly water, saline solution and/or phosphate buffer pH 7.4 and between 0.1 and 30% DMSO, more particularly 1 to 10% by weight of the composition and stabilizing or preservative agents, if required.

34. COMPOSITION of claim 23, comprising about 0.0001 to 250 mg, more particularly about 0.1 to 100 mg of at least one compound of claims 1 to 22 or one of its pharmaceutically acceptable salts or adducts.

35. COMPOSITION of claim 23, which inhibits the activity of proteins linked to disturbances or diseases.

36. COMPOSITION of claim 35, in which the protein is an enzyme.

37. COMPOSITION of claim 36, in which the enzyme comprises enzymes from the cysteine-protease, serine peptidase and metallo-protease families.

38. COMPOSITION of claim 37, in which the cysteine-proteases comprise Cathepsins B, H, J, L, N, S, T and C (dipeptidyl-peptidase-I), Interleukine Converter Enzyme (ICE), neutral proteases activated by calcium, Calpaine I and II, viral cysteine-proteases, such as cardiovirus endopeptidase, adenovirus endopeptidase and aphthovirus endopeptidase, and essential proteases for the life cycle of parasites such as proteases from *Plasmodium*, *Entamoebas*, *Onchoceras*, *Leishmanias*, *Haemonchus*, *Dictyostelium*, *Therilerium*, *Schistosoma* and *Tripanosoma* species.

39. COMPOSITION of claim 38, in which the enzyme is Cathepsin B, Cruzaine and Interleukine-1β Converter Enzyme.

40. COMPOSITION of claim 37, in which serine peptidases comprise dipeptidyl-peptidase IV, acylaminacyl-peptidase, oligopeptidase B and prolyl-oligopeptidase.

41. COMPOSITION of claim 37, in which the enzyme is Cathepsin D.

42. COMPOSITION of claim 37, in which metallo-proteases comprise angiotensin converting enzyme, collagenases, stromelisines, membrane type metallo-protease and genatinases.

43. COMPOSITION of claim 37, which may be useful for the treatment of disorders and diseases linked to proteins and enzymes.

44. COMPOSITION of claim 43, in which the diseases comprise diseases caused by tissue degradation such as arthritis, muscle distrophy, tumor invasion, glomerulonephrithis, bone infections by parasites, parasitomies, periodontal diseases and tumor metastasis; heart diseases involving the degradation of atrial natriuretic factor; inflammatory diseases, such as e. g. bronchitis, arthritis rheumatoid, osteoporosis, acute pancreatitis and cancer progressions; disorders such as amnesia, control of depression and blood pressure; diabetes, trypanosomiasis, Chagas disease, food disorders, bullimia nervosa and anorexia; alcoholism, diseases related to the production of cytokines and cytokine receptors, such as interleukine-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), interferon-gamma (INFN-gamma), IL-1 antatonist receptor (IL-1 RA), IL-10 and growth stimulation factor for granulocyte-macrophage colonies (GM-CSF), psychological stress, combat against infections caused by HIV virus (AIDS); inflammatory diseases of the Central Nervous System causing mieline degradation, including Multiple Sclerosis and autoimmune Encephalomielitis; cancer tumors, autoimmune diseases, tumors comprising breast, marrow, adenomas, thyroid, melanoma, gastric, bowel, gullet, thyroid tumors and neuroblastomas.

45. COMPOSITION of claim 44, in which the diseases are ascitic or solid tumors, particularly breast, marrow, adenomas, thyroid, melanoma, gastric, bowel, gullet, thyroid tumors and neuroblastomas.

46. COMPOSITION of any of claims 23 to 37, which inhibits young bone marrow cells from entering cell division (S stage).

47. COMPOSITION of any of claims 23 to 37, which is antiangiogenic.

48. COMPOSITION of any of claims 23 to 37, which is antimetastatic.

49. COMPOSITION of any of claims 23 to 37, which is useful to complement radio therapy treatments.

50. COMPOSITION of claim 23, which interacts with the DNA.

51. COMPOSITION of claim 23, which is immunomodulator.

52. COMPOSITION of any of claims 23 to 37, which comprises the total volume of blood of the recipient and active agent under concentration of about 0.01 to 200 μM, particularly 0.1 to 50 μM, more particularly between 10 and 25 μM.

53. DOSAGE UNIT comprising at least one compound of any of claims 1 to 22 or one of its pharmaceutically acceptable salts or adducts.

54. DOSAGE UNIT comprising at least one composition of any of

claims 23 to 52.

55. DOSAGE UNIT of any of claims 53 or 54, in which the quantity of compound or composition is enough to take the concentration from about to 0.01 to 200 μM, particularly 0.1 to 50 μM, more particularly from 10 to 25 μM of the active ingredient in the total volume of blood of the recipient.

56. DOSAGE UNIT of any of claims 53 to 55, which comprises solid and liquid forms.

57. DOSAGE UNIT of claim 56, which comprises dosage forms, such as capsules, tablets and powders, or in elixirs, syrups, emulsions, solutions, suspensions, mixtures and infusions.

58. DOSAGE UNIT of claim 53, in which the formulations are scheduled or delayed release.

59. DOSAGE UNIT of claim 53, which comprises at least one covering layer.

60. METHOD TO INHIBIT THE ACTIVITY OF PROTEINS linked to disorders or diseases, which comprises the administration of an efficient quantity of a compound of any of claims 1 to 22, a composition of any of claims 23 to 52 or a dosage unit of any of claims 53 to 59.

61. METHOD of claim 60, in which the protein is an enzyme.

62. METHOD TO TREAT DISORDERS AND DISEASES, which comprises the administration of an efficient quantity of a compound of any of claims 1 to 22, a composition of any of claims 23 to 52 or a dosage unit of any of claims 53 to 59.

63. METHOD FOR TREATMENT of claim 62, which may be intended to disorders and diseases linked to protein or enzyme activity.

64. METHOD of claim 60 or 62, in which the enzyme comprises the enzymes of the cysteine-protease, serine peptidase and metallo-protease families.

65. METHOD of claim 64, in which the cysteine-proteases comprise Cathepsins B, H, J, L, N, S, T and C (dipeptidyl-peptidase-I), Interleukine Converter Enzyme (ICE), neutral proteases activated by calcium, Calpaine I and II, viral cysteine-proteases, such as cardiovirus endopeptidase, adenovirus endopeptidase and aphthovirus endopeptidase, and essential proteases for the life cycle of parasites such as proteases from *Plasmodium*, *Entamoebas*, *Onchoceras*, *Leishmanias*, *Haemonchus*, *Dictyostelium*, *Therilerium*, *Schistosoma* and *Tripanosoma* species.

66. METHOD of claim 65, in which the enzyme is Cathepsin B, Cruzaine and Interleukine-1β Converter Enzyme.

67. METHOD of claim 64, in which the serine peptidases comprise dipeptidyl-peptidase IV, acylaminacyl-peptidase, oligopeptidase B and prolyl-oligopeptidase.

68. METHOD of claim 67, in which the enzyme is Cathepsin D.

69. METHOD of claim 64, in which the metallo-proteases comprise angiotensin converting enzyme, collagenases, stromelisines, membrane-type metallo-protease and genatinases.

70. METHOD of claim 63, in which the diseases comprise diseases caused by tissue degradation such as arthritis, muscle distrophy, tumor invasion, glomerulonephrithis, bone infections by parasites, parasitomies, periodontal diseases and tumor metastasis; heart diseases involving the degradation of atrial natriuretic factor; inflammatory diseases, such as e. g. bronchitis, arthritis rheumatoid, osteoporosis, acute pancreatitis and cancer progressions; disorders such as amnesia, control of depression and blood pressure; diabetes, trypanosomiasis, Chagas disease, food disorders, bullimia nervosa and anorexia; alcoholism, diseases related to the production of cytokines and cytokine receptors, such as interleukine-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), interferon-gamma (INFN-gamma), IL-1 antatonist receptor (IL-1 RA), IL-10 and growth stimulation factor for granulocyte-macrophage colonies (GM-CSF), psychological stress, combat against infections caused by HIV virus (AIDS); inflammatory diseases of the Central Nervous System causing mieline degradation, including Multiple Sclerosis and autoimmune Encephalomielitis; cancer tumors, autoimmune diseases, tumors comprising breast, marrow, adenomas, thyroid, melanoma, gastric, bowel, gullet, thyroid tumors and neuroblastomas.

71. METHOD of claim 70, in which the diseases are ascitic or solid tumors, particularly breast, marrow, adenomas, thyroid, melanoma, gastric, bowel, gullet, thyroid tumors and neuroblastomas.

72. METHOD of any of claims 60 to 63, which inhibits young bone marrow cells from entering cell division (S stage).

73. METHOD of any of claims 60 to 63, which is antiangiogenic.

74. METHOD of any of claims 60 to 63, which is antimetastatic.

75. METHOD of any of claims 60 to 63, which is useful to complement radio therapy treatments.

76. METHOD of any of claims 60 to 63, which comprises the administration of active ingredient between about 0.0001 to about 500 mg/kg of body weight, with the particular dose being about 0.0001 to 100 mg/kg and, more particularly, between 0.0001 and about 30 mg/kg.

77. METHOD of any of claims 60 to 63, which comprises the administration of enough active ingredient to take the concentration from about 0.01 to 200 μM, particularly 0.1 to 50 μM, more particularly from 10 to 25 μM of the active ingredient in the total volume of blood of the recipient.

78. METHOD of any of claims 60 to 63, in which the administration is

made by means of dosage units of any of claims 53 to 59.

79. METHOD of any of claims 60 to 63, in which the administration is continuous, non continuous or cyclic.

80. METHOD TO MODULATE THE IMMUNOLOGICAL SYSTEM, which comprises the administration of an efficient quantity of a compound of any of claims 1 to 22, a composition of any of claims 23 to 52 or a dosage unit of any of claims 53 to 59.

81. USE OF THE COMPOUND of any of claims 1 to 22 for the preparation of a composition.

82. USE of claim 81 for the manufacture of a medicine to inhibit the activity of proteins and enzymes.

83. USE OF A COMPOSITION of any of claims 23 to 52 for the preparation of a medicine to inhibit the activity of proteins and enzymes.

84 USE of any of claims 81 to 83, in which the enzyme comprises the enzymes from the cysteine-protease, serine peptidase and metallo-protease families.

85. USE of claim 84, in which the enzymes comprise Cathepsins B, H, J, L, N, S, T and C (dipeptidyl-peptidase-I), Interleukine Converter Enzyme (ICE), neutral proteases activated by calcium, Calpaine I and II, endopeptidases, viral cysteine-proteases, such as cardiovirus endopeptidase, adenovirus endopeptidase and aphthovirus endopeptidase, and essential proteases for the life cycle of parasites such as proteases from *Plasmodium*, *Entamoebas*, *Onchoceras*, *Leishmanias*, *Haemonchus*, *Dictyostelium*, *Therilerium*, *Schistosoma* and *Tripanosoma* species; Cathepsin D or Encephalinase, dipeptidyl-peptidase IV, acylaminacyl-peptidase and oligopeptidase B and prolyl-oligopeptidase; angiotensin converting enzyme, collagenases, stromelisines, membrane type metallo-protease and genatinases.

86. USE of claim 83, in which the diseases comprise diseases caused by tissue degradation such as arthritis, muscle distrophy, tumor invasion, glomerulonephrithis, bone infections by parasites, parasitomies, periodontal diseases and tumor metastasis; heart diseases involving the degradation of atrial natriuretic factor; inflammatory diseases, such as e. g. bronchitis, arthritis rheumatoid, osteoporosis, acute pancreatitis and cancer progressions; disorders such as amnesia, control of depression and blood pressure; diabetes, trypanosomiasis, Chagas disease, food disorders, bullimia nervosa and anorexia; alcoholism, diseases related to the production of cytokines and cytokine receptors, such as interleukine-6 (IL-6), tumor necrosis factor alpha (TNF-alpha), interferon-gamma (INFN-gamma), IL-1 antatonist receptor (IL-1 RA), IL-10 and growth stimulation factor for granulocyte-macrophage colonies (GM-CSF), psychological stress, combat against infections caused by HIV virus (AIDS); inflammatory diseases of the Central Nervous System causing mieline degradation, including Multiple Sclerosis and autoimmune Encephalomielitis; cancer tumors, autoimmune diseases, tumors comprising

ascitic or solid, breast, marrow, adenomas, thyroid, melanoma, gastric, bowel, gullet, thyroid tumors and neuroblastomas.

87. USE of any of claims 81 or 83 for the manufacture of a medicine to treat disorders and diseases linked to the protein or enzyme activity.

88. USE of any of claims 81 or 83, which inhibits young bone marrow cells from entering cell division (S stage).

89. USE of any of claims 81 or 83, which is antiangiogenic.

90. USE of any of claims 81 or 83, which is antimetastatic.

91. USE of any of claims 81 or 83 to complement radio therapy treatments.

92. USE of any of claims 81 or 83, which interacts with the DNA.

93. USE of any of claims 81 or 83, which is immunomodulator.